REVIEW ARTICLE

Twin Studies in Sleep Medicine: A Review

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ABSTRACT

Sleep and sleep disorders are complex phenotypes with genetic, epigenetic, and environmental influences. Twin studies allow researchers to parse out how these factors influence variability in sleep outcomes such as sleep duration and quality, chronotype, and disorders such as insomnia, hypersomnia, sleep apnea, sleep-related movement disorders, and parasomnias. Twin studies assess the overlap in genetic influences for sleep variance and other medical and psychiatric disorders and allow exploration of gene-environment interactions. Longitudinal twin studies demonstrate how these interactions change over the course of a lifetime. In general, twin studies demonstrate that the heritability of common sleep measures such as duration, quality, and chronotype is about 30-50%; however, this can vary widely between samples according to age, sex, comorbidities, and geographic location. Similarly, the heritability of sleep disorders including insomnia, obstructive sleep apnea, and parasomnias is also around 30-50%, with higher estimates for disorders known to run in families, such as sleepwalking. Heritability estimates for medical and psychiatric problems including obesity, depression, post-traumatic stress disorder, and mortality are higher with short sleep duration (typically < 7 h/n), suggesting that short sleep activates disease-related gene expression. Significant genetic overlap exists between insomnia and issues such as obesity, chronic pain, depression, and psychosis. In this review, we describe the major findings of twin studies related to sleep and how they impact our understanding of this critical component of health and disease.

INTRODUCTION

Over the past several decades, a growing body of evidence has highlighted the variability of sleep and sleep disorder characteristics between individuals. Significant variation is seen with normal parameters of sleep such as duration,[1] timing,[2] architecture,[3] and quality,[4,5] as well as phenotypes for sleep disorders such as insomnia,[6] obstructive sleep apnea (OSA),[7] restless legs syndrome (RLS),[8] circadian rhythms,[9] and bruxism.[10] Molecular genetic studies have identified numerous polymorphisms and other variants likely contributing to these phenotypes; however, it is clear that environmental influences also play a role in the inter-individual variability of many sleep characteristics. Twin studies provide unique insights in this regard because they allow researchers to investigate the relative contributions of genetic and environmental influences on trait variability.[11]

Numerous twin studies have identified the heritability, gene-environment interactions, and gene-environment correlations for both normal and pathologic sleep phenotypes.[12–17] Twin studies have also examined associations between sleep phenotypes and other health-related traits and disorder phenotypes,[18–22] many of which either impact sleep or are impacted by sleep. This provides an important body of work highlighting the complexity of genetic and environment interplay between sleep and health. Twin studies inform clinical classification of sleep disorders and thus may help identify precision treatments for these disorders.

The purpose of this review is to provide an overview of the methodologies and goals of twin studies, identify major areas of sleep research involving twin studies, and review the findings that add most to our understanding about the underlying mechanisms of sleep, sleep disorders, and relationships between sleep variability and health outcomes.

TWIN STUDY METHODOLOGIES

Twin studies provided the earliest investigations regarding the role of genetic and environmental factors in the development of a disorder or trait. These studies use the known correlations between monozygotic (MZ, identical) and dizygotic (DZ, fraternal) twins to determine the relative contributions of additive genetic (A), common environmental (C), and unique environmental (E) influences on a trait, as illustrated in Figure 1. MZ twins share essentially 100% of their genetic makeup, whereas DZ twins share 50% of their genes on average, as well as many shared environmental influences such as family relationships, exposure to pollution and crime, and schooling environment. Using these assumptions, it is possible to calculate the extent to which each of these "ACE" components contribute to variance of the phenotype of interest.[11,23]

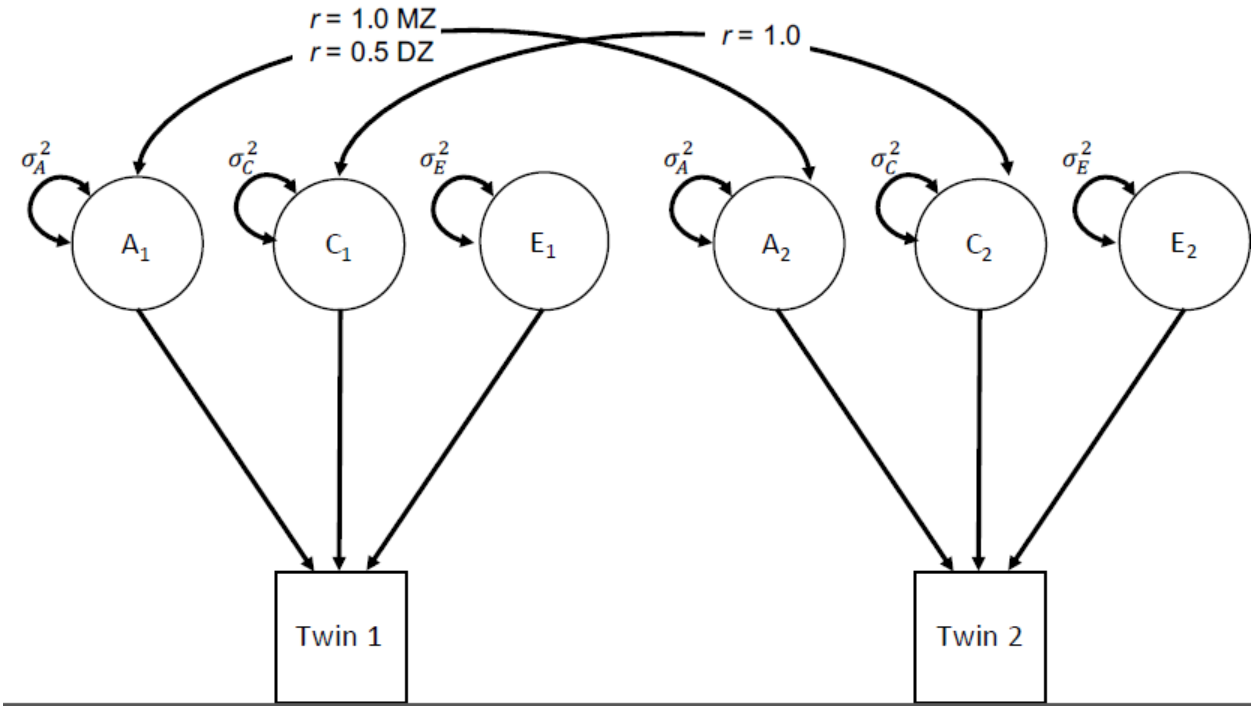

Figure 1 – Classical univariate model for a single variable. In the traditional univariate "ACE" model, the variance of the observed variable is decomposed into three components: additive genetic influences, A (σ^2_A), shared environmental influences, C (σ^2_C), and non-shared environmental influences, E (σ^2_E). The twin analysis assumes a correlation of 1 between MZ co-twins and 0.5 between DZ co-twins for additive genetic influences, a correlation of 1 between all twin pairs for shared environmental influences, and a correlation of 0 for non-shared environmental influences.

Multivariate analyses add another layer of complexity by calculating the correlations between ACE components for multiple variables of interest. (Figure 2)

Using this information, an estimate of the "heritability" of a specific trait can be computed. Twin studies can also be used to investigate the gene-environment interactions (GxE) and gene-environment correlations (rGE). GxE indicates how genetic influences on a trait vary as a function of an environmental exposure, and vice versa (for example, short sleep duration possibly leading to increased body weight through expression of genetic risk variants). rGE refers to the influence of genetic factors on subsequent environmental exposures (for example, a genetic predisposition for anxiety may lead to excessive rumination in bed and subsequent insomnia). Furthermore, twin studies can delineate heterogeneity between subtypes of a phenotype or disorder that may be caused by different biological mechanisms. For example, finding different levels of genetic influences in different populations may suggest distinct pathophysiological causes. This type of analysis may be helpful in identifying specific phenotypes of sleep disorders, such as insomnia or sleep apnea, and offer avenues for identifying optimal treatments for those phenotypes. Analyzing gene-environment interactions longitudinally also allows a better understanding of how ACE influences on phenotypic variance change throughout the lifespan (for example, with chronotype during adolescence and middle age).

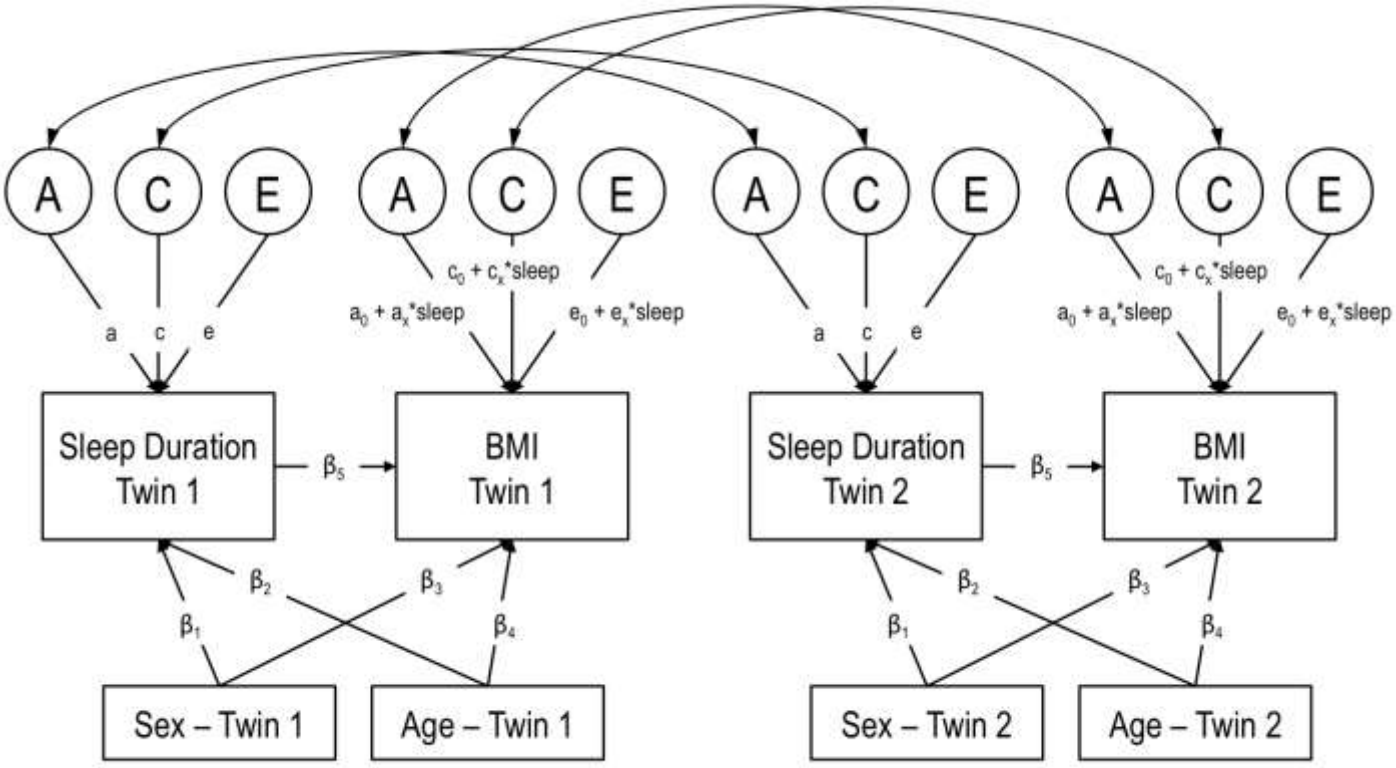

Figure 2 – Example of a multivariate structural equation model of sleep duration and BMI in adult twins. Analyses such as these allow assessment of gene-environment interactions. A, additive genetic variance; C, shared environmental variance; E, nonshared environmental variance. A, C, and E components are standardized (mean = 0, standard deviation = 1). Correlations between A components are fixed at 1.0 in monozygotic twins and 0.5 in dizygotic twins. Correlations between C components are fixed to 1.0 in all twins. Correlations between E components are fixed to 0 in all twins. The key values of interest here are the interaction parameters (a_x, c_x, and e_x). Significant values for the interaction parameters indicate that the magnitude of genetic and environmental influences on BMI differs with sleep duration, with positive values indicating greater influence with greater sleep duration and negative values indicating less influence with greater sleep duration. All variables were standardized prior to the analysis; therefore, the values of a_0, c_0, and e_0 represent the influence of genetic, shared environmental, and nonshared environmental influences, respectively, when sleep duration equals the sample mean. Lastly, the main effect of sleep duration on BMI was also estimated (the arrow labeled β_5 above). The main effect of age was estimated by the arrows labeled β_2 and β_4 and sex by the arrows labeled β_1 and β_3, respectively, for both twin 1 and twin 2. *From: Watson NF, Harden KP, Buchwald D, et al. Sleep duration and body mass index in twins: A gene-environment interaction. Sleep. 2012;35(5):597-603.*[19]

Finally, twin studies are used to analyze associations between exposures and sleep-related outcomes. Epidemiological association studies allow researchers to examine between-twin "phenotypic" associations and within-twin "quasi-causal" models.[23,24] These models can be used to examine associations between multiple phenotypes, including the extent to which one trait modifies the contributions to variance in the other trait (for example, whether the sleep duration-obstructive sleep apnea association is modified by physical activity level), and the overlap between genetic influences on variance of both traits (for example, whether there is an overlap of

genetic influences on the variance of insomnia and post-traumatic stress disorder). Significant genetic covariation between multiple conditions may also inform molecular genetics studies on candidate gene variants and genome-wide association studies (e.g., significant genetic covariation between phenotypes would suggest that genes known to influence one phenotype could be investigated for the other phenotype).

In the following review, we will discuss twin studies focusing on the importance of variation in typical sleep parameters, such as sleep duration, architecture, and quality, on health-related outcomes. We will then review the major findings of twin studies related to sleep disorders.

METHODS

We performed a standardized literature search for relevant twin study papers in the Pubmed database (https://www.ncbi.nlm.nih.gov/pubmed/). The initial search was performed on March 12, 2021. The following keywords were used to search titles and abstracts: twin AND (sleep OR insomnia OR apnea OR hypoventilation OR snoring OR narcolepsy OR hypersomnia OR circadian OR phase OR chronotype OR diurnal OR parasomnia OR nightmare OR restless OR periodic OR bruxism). This produced the following results:

1. 1,727 publications identified and screened in Pubmed
2. 1,530 excluded after abstract screening:
- Did not pertain predominantly to sleep-wake
- Were not in English
- Animal studies
- Did not use a twin sample
3. 197 publications reviewed

Thirteen pertinent manuscripts referenced in search result papers but not located in Pubmed were later reviewed as appropriate.

SLEEP DURATION

It has been well-established that extremes of sleep duration (sleeping less than 7 hours/night or more than 9 hours/night) are associated with a variety of poor medical and psychiatric health outcomes, including risk for hypertension,[25] acute coronary events,[26] diabetes,[27] cognitive problems, motor vehicle accidents, impaired judgement,[28] and mortality.[29] The relative contributions of genetics versus environment factors on variation of sleep duration is thus of great interest.

Despite the common perception that "habitual" sleep duration is a choice or is constrained by lifestyle factors, there is substantial evidence showing that it is at least partly determined by genetic influences. A recent systematic review and meta-analysis of 19 independent samples of 45,328 twins between the ages of 6 months and 88 years by Kocevska and colleagues found an overall MZ twin correlation of 0.63 (SD 0.12) and an overall DZ twin correlation of 0.40 (SD 0.10). Based on these meta-analyzed correlations, the overall heritability estimate for sleep duration was 46%. This indicates that approximately 46% of the variance in sleep duration, on average, is genetically determined. The remaining variation in sleep duration was almost entirely attributed to unique environmental factors (54%), with negligible variance due to shared environment. Heterogeneity was high (I^2 = 98%) for correlations in both MZ and DZ twins.[12] A separate systematic review and meta-analysis published in 2020 by Madrid-Valero and colleagues, including 13 studies of twins aged 6 years and older, found a similar mean sleep duration heritability of

38%. Heterogeneity was also high in this analysis ($I^2 = 99.73$).[13]

When examining individual twin studies on sleep duration, there is a wide range of heritability estimates, from as little as 0% [30] to as high as 71%.[31] (Table 1) Some of this variability may be accounted for by differences in the sample demographics, such as age, sex, comorbidities, and location. In particular, both sleep duration itself and heritability of sleep duration may change over the lifespan.[32] The recommended sleep duration for infants is 14-17 hours, preschoolers 10-13 hours, school-aged children 9-11 hours, teenagers 8-10 hours, and adults 7 or more hours.[33,34] The meta-analysis of sleep duration by Kocevska et al found that heritability estimates for sleep duration were lowest in infancy and early childhood (17% and 20% respectively), increased to 41% - 52% in middle childhood, up to 69% in adolescence, and again decreased in adulthood to 42-45%.[12] In contrast, the meta-analysis by Madrid-Valero et al, did not find significant differences in heritability between age groups in any of their models. Of note, this meta-analysis did not include studies with children younger than 6 years.[13]

Table 1. Twin studies on heritability of sleep duration.

Authors	Year	Country	Measure	Age, mean years (range)	H^2
Åkerstedt et al[18]	2017	Sweden	Self-report	71	All: 0.28 Sleep <6.5 h/n: 0.86 Sleep ≥9.5 h/n: 0.42
Barclay et al[30]	2010	UK	Self-report	20 (18-27)	0
Breitenstein et al[106]	2018	USA	Actigraphy	1-5	0.15-0.36
Brescianini et al[107]	2011	Italy	Parent-report	1.5	0.31
Butkovic et al[42]	2014	Croatia	Self-report	15-22	0.63
De Castro[108]	2002	USA	Diary	41.9	0.30
Fisher et al[109]	2012	UK	Parent-report	1.3 (1.2-2.3)	0.26
Gedda & Brenci[110]	1979	Italy	Self-report	6-8, 16-18	Ages 6-8: 0 Ages 16-18: 0.23
Genderson et al[111]	2013	USA	Self-report	55.4 (51-60)	0.29
Gehrman et al[112]	2019	USA	Actigraphy	16-40	0.49
Gregory et al[31]	2006	UK	Child-report Parent-report	8 (8.2-8.9)	Child-report: 0.01 Parent report: 0.71
Heath et al[113]	1990	Australia	Self-report	17-88	0.09
Hublin et al[114]	2013	Finland	Self-report	Over 18	0.30-0.32
Inderkum et al[115]	2018	Switzerland	Actigraphy	12.8	0.15-0.68
Liu et al[116]	2012	China	Self-report	21-72	0.27-0.29
Lopez-Minguez et al[117]	2017	Spain	Actigraphy	52	0.65
Madrid-Valero et al[118]	2018	Spain	Self-report	53.7 (41-73)	0.30
Partinen et al[119]	1983	Finland	Self-report	18 and over	0.44
Sletten et al[120]	2013	Australia	Actigraphy	12.2	0.65
Te Velde et al[121]	2013	Netherlands	Self-report	16.9 (12-20)	0.34-0.36
Touchette et al[122]	2013	Canada	Parent-report	0.5-4	0.47-0.58
Watson et al[123]	2010	USA	Self-report	36.9	0.31

It has been theorized that changes in the heritability of sleep duration over the lifespan found in some of these studies may be related to the fact that, unlike many other aspects of sleep, sleep duration is partially under voluntary control.[35] The impact of genetic influences may be attenuated in adults by societal pressures and obligations. Likewise, in children, sleep timing and duration may be influenced heavily by parental constraints. Changes in heritability over the lifespan have also been observed with other traits, such as chronotype, weight, temperament, and intelligence quotient.[36,37]

In contrast to differences in age seen with sleep duration heritability, twin studies have typically not found a significant difference in heritability between men and women. Sleep duration heritability was not significantly different by sex for either of the large meta-analyses performed in 2020 and 2021.[12,13] This is also in line with a previous genome-wide association study of twin-based heritability for sleep duration, which showed a high genetic correlation ($r_g = 0.989$) between men and women.[1]

A potential difference between twin studies that may impact heritability is the method of sleep duration measurement. Some studies use subjective sleep duration as recorded on various measures: a single self-reported average over a typical week or on a typical night, sleep duration averaged from entries in a sleep diary, self-reported on a screening questionnaire such as the Pittsburgh Sleep Quality Index (PSQI), or even reported by another person such as a parent. Other studies have reported objective sleep duration as measured by polysomnography (PSG) or actigraphy. Objective measurements may provide a more accurate value for sleep duration; however, measures such as PSG may also introduce disruptive factors leading to deviation from the "habitual" duration occurring in the participants' normal sleep environment. In the meta-analysis by Kocevska et al, sleep duration heritability was highest for actigraphically-measured sleep duration (100%), moderate for self-reported (38%) and sleep diary-reported sleep duration (52%), and lowest for PSG-measured (27%) and parent-reported sleep duration (8%).[12] Differences in heritability between measurements may reflect the relative accuracy of the measure (for example, objective versus subjective accuracy, or self- versus parent-reported duration). Differences in heritability may also indicate different measures are actually recording different parameters (for example, sleep perception for self-report measures or inactivity for actigraphy).

Other factors that might impact the heritability of sleep duration include location, cultural factors, and socioeconomic status. A study of the Washington State Twin Registry found area-level deprivation, as indicated by the Singh Index, predicts shorter sleep duration. The uncontrolled phenotypic regression of sleep duration on the Singh Index showed a significant negative relationship between area-level deprivation and sleep length, with every 1 standard deviation in Singh Index being associated with a ~4.5 min change in sleep duration.[38]

Twin studies that specifically include samples with medical and psychiatric comorbidities have reported complex interactions between these comorbidities and sleep duration. A number of these studies have shown the "U-shaped" association between sleep duration and adverse health conditions that has been consistently shown in other types of research. Many of these studies also highlight the influence of sleep duration on the heritability of these comorbidities, and vice versa.

Medical comorbidities and overall mortality

One prospective twin study using 14,267 twins from the Swedish Twin

Registry found a clear U-shaped curve between sleep duration and mortality. The heritability of mortality for the entire sample was 28%, but was 86% for short sleepers and 42% for long sleepers, suggesting that environmental factors played a greater role in mortality for long sleepers, whereas genetic influences dominate for mortality in short sleepers.[18]

A gene-environment interaction was found specifically for self-reported body mass index (BMI) and sleep duration using the Washington State Twin Registry, such that the heritability of BMI with short sleep duration (h^2 = 70% for < 7 h/n) was twice as large as the BMI heritability with longer sleep duration (h^2 = 32% for ≥ 9 h/n).[19] This suggests short sleep turns on obesogenic gene expression.

Potential mechanisms for adverse metabolic and cardiovascular outcomes with short sleep duration were obtained from a co-twin study of 11 sleep duration-discordant MZ twin pairs that found distinctive gene regulation differences based on sleep duration. Habitual short sleep was associated with upregulation of immunoinflammatory pathways such as interleukin signaling and leukocyte activation, as well as developmental processes, the coagulation cascade, and cell adhesion.[39] Another study with 15 sleep duration-discordant MZ twin pairs found reduced sleep duration was associated with reduced mitochondrial DNA copy number; the authors suggested this may be another potential mechanism by which short sleep impairs health and longevity through mitochondrial stress.[40]

Mental health comorbidities

Twin studies have also examined the gene-environment interactions between sleep duration and mental health. Short sleep duration has been associated with greater depressive symptoms, with greater depression heritability at sleep duration extremes in adults (with heritability of 53% for 5 h/n and 49% for 10 h/n, compared to 27% for 7-8.5 h/n).[20] A relationship between depressive symptoms and sleep duration was also found in adolescent twins, for whom within-twin pair differences showed sleep duration was positively associated with self-control, and negatively associated with depressive symptoms.[41] Adolescents with shorter sleep duration (<6.5 h/n) also scored higher on neuroticism scales, and those associations were mediated most by overlapping genetic factors.[42]

Our twin study on self-reported post-traumatic stress disorder (PTSD) symptoms and sleep duration showed a U-shaped curve between sleep duration and PTSD symptoms. We also found a bidirectional moderating relationship between PTSD symptoms and sleep duration, such that as PTSD symptom severity increased, the influence of shared environmental influences on sleep duration also increased. Conversely, as sleep duration decreased, the influence of genetic factors on PTSD symptoms increased.[21] This suggests that early life experiences may increase variability in sleep duration later in life in trauma-exposed individuals, and that genetic factors predisposing to a pathologic stress response are affected by short sleep duration.

SLEEP QUALITY

Another large body of twin studies has focused on the heritability and gene-environment interactions of sleep quality. Unlike studies on sleep duration, measures for sleep quality are typically only subjective and may include a single question or standardized measures such as the PSQI. (Table 2)

Table 2. Twin studies on heritability of sleep quality.

Authors	Year	Country	Measure	Age, mean years (range)	H^2
Barclay et al[30]	2010	UK	PSQI sleep quality	20 (18-27)	0.43
Barclay et al[59]	2010	UK	PSQI	20 (18-27)	0.41
Boomsma et al[43]	2008	Netherlands	Dutch Groningen Sleep Questionnaire	31	0
Gasperi et al[50]	2017	USA	PSQI	29 (19-65)	0.36
Genderson et al[111]	2013	USA	PSQI	55.4 (51-60)	0.34
Gregory et al[48]	2017	UK	PSQI	18	0.33
Heath et al[113]	1990	Australia	Single item	17-88	0.32
Hu et al[54]	2020	US	PSQI	53.5 (34-82)	0.26
Madrid-Valero et al[118]	2018	Spain	PSQI	53.7 (41-73)	0.31-0.34
Paunio et al[124]	2009	Finland	Single item	33 (18-95)	0.33-0.53
Taylor et al[49]	2015	UK	PSQI	16	0.41

A meta-analysis of sleep quality amongst 10 independent samples (39,020 twins between 16 and 95 years) found 44% of the variability in sleep quality is genetically determined. MZ twin correlations ranged from 0.20-0.68, and DZ twin correlations ranged from 0.06-0.27. The magnitude of the difference between MZ and DZ twin correlations indicates only a small contribution from shared environmental influences to sleep quality variance, with non-shared environmental influences primarily contributing to the remaining 56%. Heterogeneity was relatively high for correlations in both monozygotic (I^2 = 60%) and dizygotic (I^2 = 75%) twins. In this analysis, age and sex did not moderate the MZ or DZ correlations; however, the samples did not include twins younger than 16, and so it is unclear if heritability estimates would differ in children and adolescents.[12]

Another recent meta-analysis of 10 studies found a mean heritability of 31% (range 0-43%), with a high heterogeneity index (I^2 = 98.77). Age and sex were also not found to be significant moderators for heritability, similar to the other meta-analysis. The remainder of the variance in sleep quality was due to non-shared environmental influences.[13] Despite the heterogeneity noted in these studies, the presence of significant heritability estimates across the 10 studies was relatively consistent, except in one study in which all of the variance was accounted for by non-shared environmental influences. However, this study assessed sleep quality using a diary for only a single night, which may not adequately reflect habitual sleep quality.[43]

The importance of non-shared environmental influences on the variability of sleep quality has been noted in many twin studies. A MZ twin differences design assessed the contribution of non-shared environmental influences through the PSQI and questionnaires assessing several potential "environmental" measures. When controlling for genetic and shared environmental effects, within-pair differences in sleep quality were associated with within-pair differences in general health for males and relationship satisfaction in females. All other environmental measures investigated did not remain significantly associated with sleep quality when genetic and shared environmental factors were controlled, which suggests their associations with sleep quality may be dependent on genetics and/or the shared environment.[44]

A limitation of studies on sleep quality is that the specific etiology of disturbed sleep is not known. Sleep quality

may be impaired for a wide number of reasons, including sleep disorders such as sleep apnea, insomnia, parasomnias, or restless legs; medical reasons such as chronic pain or cardiopulmonary disease; medications; or psychiatric problems such as anxiety, PTSD, or attention-deficit hyperactivity disorder (ADHD). Given the broadness of the differential diagnoses, it is difficult to know what the heritability is truly measuring. Studies looking at shared genetic overlap between sleep quality and another comorbidity may shed some light on potential etiologies of the sleep quality problem.

Similarly to sleep duration, twin studies on sleep quality have also investigated correlations with other traits and disorders, as we will review in the following sections.

Medical comorbidities

Poor quality sleep is known to co-occur with medical problems, including pain. A study of the Murcia Twin Registry found a phenotypic correlation between sleep quality and low back pain of 23%. The correlation between genetic factors influencing each trait was 0.33, and genetic overlap explained 42.5% of the phenotype correlation.[45] Another study of neck pain and sleep quality found chronic neck pain was significantly associated with poor sleep quality in the total sample analysis, discordant analysis, and in DZ pairs, but not in MZ pairs. The authors concluded that the association between sleep quality and chronic neck pain is partially confounded by genetic factors.[46]

Other than pain, twin studies have also focused on gene-environment relationships with sleep quality and health risks. A co-twin study found that sleep quality and BMI showed an inverse relationship. For BMI-discordant twins, this association maintained a similar effect size and significance; however, for sleep quality-discordant twins the association lost significance. The authors suggest there is a directionality to this relationship such that sleep quality may impact BMI, but not vice versa.[47]

Mental health comorbidities

Many studies have also found genetic overlap between sleep quality and psychiatric disorders. A longitudinal study on 5-18 year-old twins with ADHD found an association between ADHD and poor sleep quality that was 55% due to genetic influences and 45% due to non-shared environmental influences.[48]

Taylor and colleagues found moderate overlap between both genetic (r_A = 0.48-0.56) and environmental (r_E = 0.20-0.28) influences of psychotic-like symptoms (such as paranoia, hallucinations, and grandiosity) and those of sleep quality.[49]

Shared genetic influence has also been studied between sleep quality and both anxiety and depression. Twin studies have found a genetic correlation of 61%-73% between depression and sleep quality.[50,51] A study of young adult twins and sibling pairs also found a 58% overlap in genes influencing sleep disturbance and anxiety. The associations between sleep disturbance and symptoms of anxiety and depression explained 74% and 58% of the covariance, respectively, with the remainder explained by non-shared environmental influences.[52]

A study looking at insomnia, sleep quality, depression, anxiety, and anxiety sensitivity traits in adolescent twins found moderate genetic correlations between sleep quality and anxiety (rA = 0.61) as well as anxiety sensitivity (rA = 0.52).[51] Another study of adolescent twins in the Italian Twin Registry found a significant association between sleep quality and emotional regulation that was explained by genetic and shared environmental factors.[53]

In middle-aged and older adult twins, a co-twin design found that the genetic and shared environmental components of perceived stress explained 8% of the variance in sleep quality and the individual-specific component of perceived stress explained another ~8% of the variance in sleep quality, suggesting genetic, shared, and individual factors explain an equivalent proportion of the stress-sleep relationship.[54]

CIRCADIAN RHYTHMS OF SLEEP AND WAKE

Twin studies in the realm of chronobiology have focused primarily on the heritability of circadian timing and chronotype. Studies of biological markers of circadian patterns such as body temperature parameters, cortisol rhythms, bioelectrical impedance-derived phase angle, melatonin secretion, and light sensitivity have found genetic factors account for a significant portion of the variance in circadian patterns.[55–58]

Chronotype, also known as diurnal preference, is an individual's tendency to be most awake/alert in the evening ("eveningness") or morning ("morningness"). Twin studies suggest there is a genetic component in chronotype, with heritability estimates ranging from 44%-50%.[17,59–61] Given that circadian rhythmicity is also strongly impacted by behavioral patterns (such as light exposure, food intake, physical activity, and social interaction), there has also been interest in identifying the contributions of non-shared environmental contributors to variance. Barclay and colleagues found within-pair differences in chronotype were associated with within-pair differences in negative life events, educational level, smoking status, and drug use.[62] Additionally, genetic influences on chronotype were found to be attenuated during middle adulthood relative to younger and older adulthood, possibly driven by the increased importance of work and family responsibilities, at the expense of optimal sleep timing, during middle age.[36] Epigenetic differences in DNA methylation may also mediate this relationship; a twin study of 15 MZ twin pairs found DNA methylation differences in twins discordant for chronotype.[63]

Evening chronotype has been associated with numerous medical and psychiatric disorders.[59] Twin studies on chronotype have also found significant genetic overlap between eveningness and depression, poor sleep quality, problematic alcohol use, and smoking.[22,64,65] A study on twin shift workers in the Older Finnish Twin Registry also found that individuals with an evening chronotype had a significantly increased risk of prostate cancer; however, there was no significant association between sleep or circadian parameters and risk in co-twin analyses.[66] The link between shift work, which itself is associated with numerous negative aspects of sleep, and incident cancer has been well-established,[67] but studies have not yet delineated a genetic role in this phenomenon.

SLEEP DISORDERS

In the following sections, we will discuss twin findings with respect to the most prevalent sleep disorders according to their classification in the International Classification of Sleep Disorders (ICSD), Third Edition.[68]

Insomnia

Twin studies have consistently found that additive genetic factors contribute to insomnia variability, though with a wide range of estimated heritability as noted below. Insomnia symptom phenotypes may vary based on the specific symptoms reported; individuals with insomnia may experience difficulty getting to sleep, difficulty maintaining sleep, waking up too

early, or some combination of these symptoms. Previous editions of the ICSD defined several subtypes of insomnia according to symptoms, presumed etiology, and age group; however, these phenotypes have been combined in the most recent diagnostic classification.[68]

A 2021 meta-analysis by Madrid-Valero and colleagues of 10 international studies found an overall heritability of 39%, with individual studies ranging from 28%-57%, and non-shared environmental influences being the largest source of insomnia variance with values ranging from 43%-72%. This analysis excluded studies using indirect measures not specifically referred to as insomnia symptoms, as well as studies with a mean sample age < 6 years, which limits the findings. Although the authors found high heterogeneity amongst the samples, moderators such as age, sex, continent, or type of measure was found to explain differences in variance between studies.[69]

Another meta-analysis by Barclay and colleagues in 2020 found a similar heritability of 40% from MZ and DZ correlations in 12 papers. This analysis showed higher heritability for women compared to men, and for parent-reported insomnia compared with self-reported measures. They did not find significant differences in heritability between various insomnia symptoms, but noted there was a broad range between studies for difficulty initiating sleep (0-79%) and difficulty staying asleep (25-42%), with fewer studies evaluating early morning awakenings (34-35% in one study) and awakening tired (26% in one study).[14]

Studies looking at pre-sleep arousal and sleep reactivity have also found substantial genetic overlap with insomnia, indicating possible enhanced vulnerability to insomnia occurring with these symptoms. A longitudinal twin and sibling study found a strong correlation between genetic influences on overall pre-sleep arousal and insomnia symptoms (genetic correlation = 0.88), as well as between cognitive pre-sleep arousal, somatic pre-sleep arousal, and insomnia symptoms (genetic correlations 0.93 to 1).[70] A study on sleep reactivity using the Ford Insomnia Response to Stress Test (FIRST) found the genetic variances in insomnia and FIRST scores were correlated (r = 0.54 in females, r = 0.64 in males), as were the environmental variances.[71] Findings such as these lend support to insomnia models such as Spielman's 3P model of insomnia, which hypothesizes that chronic insomnia derives from predisposing factors, precipitating factors, and perpetuating factors.[72] Predisposing factors are presumed to be a combination of biological factors such as increased baseline hyperreactivity and tendency towards worry, which may be mediated by genetic influences.

Insomnia symptoms are also frequently comorbid with psychiatric disorders as well as medical problems such as chronic fatigue, obesity, and pain. Twin studies have shown substantial genetic overlap between these comorbidities as well.[49,51,73–76]

Genetic correlations between insomnia and depression phenotypes have been found to be high (0.73-1.00),[51,73] with genetic influences accounting for 50% to 90% of the overlap in one study.[73] A study by Gehrman and colleagues of twins aged 8-16 years also found a genetic overlap between insomnia, depression, and anxiety. In fact, they did not find evidence for any role of genetic factors for insomnia variance that did not overlap with depression or anxiety, with their model supporting a greater influence of non-shared environmental factors.[75] Madrid-Valero also found high genetic overlap between insomnia and anxiety (rA = 0.59).[51]

Taylor and colleagues found significant genetic correlations between

insomnia and paranoia, hallucinations, and cognitive disorganization.[49] Cox and colleagues studied gene-environment interactions between post-traumatic intrusion symptoms, avoidance symptoms, and insomnia in 242 twin pairs with trauma exposure, and found genetic correlations of 0.50 between insomnia and intrusions, and 0.49 between insomnia and avoidance symptoms.[77]

Twin studies on general medical problems have also found associations with insomnia. Watson and colleagues found that genetic factors accounted for 10% of the correlation between insomnia and obesity.[76] Another study examined the shared genetic and environmental factors underlying the association between insomnia, pain, and other somatic symptoms. The authors studied adolescents and their parents and found significant phenotypic associations between insomnia severity and both pain and somatic measures, with genetic factors accounting for 41%- 86% of the correlations.[74]

Hypersomnia Disorders

Hypersomnia can occur for a variety of reasons, including insufficient sleep duration, poor sleep quality due to another factor such as obstructive sleep apnea, or a central nervous system hypersomnia disorder such as narcolepsy. Sleepiness itself may be influenced by genetic factors, as evidenced by a twin studies finding heritability estimates of 38%-40%.[76,78]

Genetic studies on hypersomnia have primarily focused on narcolepsy, a central nervous system hypersomnia disorder characterized by daily episodes of irresistible sleepiness, and diagnosed by a daytime nap test showing objective sleepiness as well as the presence of rapid eye movement (REM) sleep intrusion during naps.[68] Narcolepsy phenotypes may vary based on the presence of cataplexy, a symptom of muscle atonia triggered by emotions, as well as other symptoms of REM intrusion such as sleep paralysis and hallucinations upon waking/sleep onset.

Narcolepsy is a rare disorder, occurring in only 0.03–0.1% of the general population. However, in first-degree relatives the risk of developing narcolepsy is estimated at 1-2%, which is 20-40 times higher than the general population.[79] Due to the relative rarity of the disorder, large twin studies are not possible, with most investigations focusing on individual twin pairs.[80] A study in 1994 detailed the authors' unsuccessful efforts to find even one twin case suggestive of narcolepsy in the Finish Twin Cohort.[15] Only 25-31% of the MZ twins reported are concordant for narcolepsy, suggesting environmental factors may play a significant role in the development of the disorder. This is consistent with the current conceptualization that type I narcolepsy is an auto-immune disease driven by molecular mimicry.[81,82]

Twin studies of narcolepsy have also been used to look for specific genetic variants. While molecular studies have found associations with the HLA-DQB1*0602 allele and other specific HLA variants, only three of eight narcolepsy-concordant twin pairs have been found to be positive for these alleles.[79,83] A study of two narcolepsy-discordant HLA-DR2+ MZ twin pairs and their families showed two HLA DR2+ relatives with short nap latencies, as well as abnormal REM periods during naps in a relative who was HLA DR2-.[84] This would suggest other, hitherto unknown genes may contribute to narcolepsy.

A case report of early childhood onset in a MZ twin pair discordant for narcolepsy found the only environmental difference between the 5-year-old co-twins was a head injury.[85] A case of incomplete concordance of narcolepsy was reported in which one twin did not experience narcolepsy symptom onset until age 45, the onset of which was attributed

to chronic emotional stress and sleep insufficiency.[86] These reports, while limited, also emphasize the potential role of non-shared environmental influences on the development of narcolepsy.

Kleine-Levin syndrome is an even rarer form of hypersomnia characterized by recurrent periods of profound sleepiness, cognitive disturbances, and behavioral disinhibition. The etiology of this disorder is poorly understood. A case report of Kleine-Levin occurring in 16 year-old MZ twin boys indicated both boys suffered first episodes after an influenza infection. HLA testing was negative for DQB1*02 loci, and no additional genetic cause was revealed.[87]

Obstructive Sleep Apnea

OSA is a sleep-related breathing disorder characterized by intermittent partial or total collapse of the upper airway during sleep, leading to oxygen desaturations, sleep fragmentation, and associated health risks.[68] Genetic predisposing factors such as mandibular size, fat deposition around the airway, and respiratory drive may contribute to the development of OSA. Environmental factors may include nutrition and calorie intake, alcohol use, and lack of physical exercise.

Twin studies using self-report measures of snoring or symptoms of OSA have shown heritability of up to 50%.[16,78] A twin study of 71 twin pairs from the Hungarian Twin Registry underwent overnight PSG to provide objective data. Heritability of the apnea-hypopnea index (AHI), respiratory disturbance index (RDI), and oxygen desaturation index (ODI) ranged from 69% and 83%. The presence of AHI ≥ 5/h was 73% heritable. The rest of the variance was attributable to non-shared environmental factors.[88] Another sample of World War II male twin pairs underwent unattended Edentrace recordings, with resulting heritability estimates of 37% for RDI, 36% for ODI, and 10% for minimum oxygen saturation.[89] The difference in heritability between these studies may reflect heterogeneity in age and measurement type.

In adolescent twins and siblings, genetic influences were found to account for about 40% of sleep apnea symptom variance, with moderate associations between OSA and depression/anxiety (r = 0.22-0.29); 95% of the covariation between depression and sleep apnea symptoms was due to genetic influences.[90]

Sleep-Related Movement Disorders

Movement disorders of sleep include RLS, periodic leg movements, and bruxism. RLS has known genetic variants as identified in family and genome-wide association studies, with twin studies also showing higher concordance for RLS and growing pains in MZ than in DZ twins.[16,91–93] Champion and colleagues also analyzed twin pairs with painful versus painless RLS and found that painful RLS showed heritability, whereas painless RLS was not genetically influenced but was associated with female sex, iron deficiency, and persistent pain disorders.[8]

Sleep-related bruxism, or tooth-grinding, has been studied in several twin samples. Most of these studies showed higher concordance in MZ than DZ twins,[94–98] with one study concluding neither genetic nor shared environmental factors impact bruxism.[99] Bruxism is also associated with tobacco use, coffee, and alcohol. One study found that in MZ twins discordant for bruxism and smoking, in all cases the bruxer was the smoker.[100]

Parasomnias

Parasomnia encompass an array of sleep disorders characterized by undesirable events or experiences during sleep. They include non-REM (NREM) disorders such as sleepwalking, confusional arousals, night

terrors, and sleep-related eating disorder, as well as REM-related parasomnias such as REM sleep behavior disorder and nightmare disorder. We found only a small number of twin studies investigating these disorders.

One study of 646 twin pairs found MZ twins were concordant for sleepwalking six times as often as DZ twins.[101] A more recent and larger study found the proportion of variance attributed to genetic influences was 66% in men and 57% in women for childhood sleepwalking, and 80% in men and 36% in women for adult sleepwalking.[102]

Sleep terrors were also found to be heritable with 43.7% of variance attributable to genetic effects in 18 month-old twins, and 41.5% at 30 months of age.[103]

We found a single case study on fraternal twins, as well as their father, who all had sleep-related eating disorder. The authors noted that daytime eating disorders show higher concordance between MZ than DZ twins, suggesting sleep-related eating disorder may be similar.[104]

For nightmares, a study of the Finnish Twin Cohort found genetic influences contributed to 44% of nightmare variance in boys and 45% in girls during childhood. In adults, the estimated genetic contribution was 36% in men and 38% in women, indicating persistent genetic effects on nightmare variance through the lifetime.[105]

CONCLUSIONS

Sleep encompasses a vast number of normal and pathological processes, and has enormous impact on health and disease. Twin studies allow researchers to explore the relative genetic and environmental contributions to the complex phenotypes of normal sleep parameters as well as sleep disorders. In this review, we discussed the major research findings on heritability and gene-environment contributions to important parameters of sleep such as sleep duration and sleep quality. We also described twin studies showing genetic overlap between these parameters and other conditions frequently comorbid with sleep pathology. Finally, we discussed the major twin study findings for the most common sleep disorders. Overall, the studies reviewed demonstrate that the heritability of common sleep measures such as duration, quality, and chronotype, is about 30-50%; however, estimates vary greatly by sample characteristics.

Twin research has contributed greatly to our understanding of how genetic factors, shared environmental factors, and unique environmental factors are interrelated, and how they may change over the course of the lifespan. While molecular genetics studies increase our understanding of the specific genetic predisposition for phenotypic variance, it is clear that environmental factors also significantly influence sleep measures, as well as GxE. The information gleaned from twin studies may help to parse out the extent to which these influences interact. In the field of sleep medicine, research has begun to identify distinct phenotypes amongst heterogeneous disorders such as obstructive sleep apnea and insomnia, with a particular interest in determining the most optimal treatments for each phenotype.[6,7] The genetic and epigenetic underpinnings of these phenotypes have yet to be discovered. Twin studies can help further define and clarify sleep disorder phenotypes by analyzing the relative genetic and environmental contributions to variance, as well as identifying genetic correlations between sleep disorder phenotypes and other relevant comorbidities. As our ability to capture both genomic data and environmental factors increases through commercial and consumer technologies, twin studies may allow researchers to hone in on specific genes that contribute to each phenotype, and how their expression is modified by the environment. Ultimately, this may allow the development

of precision medicine strategies for risk reduction and treatment. Twin studies are thus an optimal complement to molecular genetic and epigenetic studies to identify the potential interactions of nature versus nurture in sleep.

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